

Application No.: 09/815,341  
Art Unit: 1631

-2-

### REMARKS

Reconsideration of the Final Office Action mailed March 12, 2004, (hereinafter "instant Office Action"), entry of the foregoing amendments, and withdrawal of the rejection of claims 21-27, 32 and 33 are respectfully requested.

In the instant Office Action, claims 1-88 are listed as pending, claims 1-20, 28-31 and 34-88 are withdrawn from consideration, claims 21-27, 32 and 33 are listed as rejected and claim 32 is objected to.

Applicants gratefully acknowledge that in the Advisory Action the Examiner has withdrawn the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, second paragraph, with respect to the term "Tie-2".

Applicants also gratefully acknowledge that the Examiner has withdrawn the objection to Claim 32.

The Examiner has maintained the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for the atomic coordinates for residues 802-1124 of Tie-2 and Inhibitor III complex, does not reasonably provide enablement for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex. Applicants respectfully traverse this rejection. Applicants maintain the arguments that were presented in the Replies mailed December 23, 2003 and July 8, 2004.

The Examiner alleges that the invention as presently stated in claim 21 encompasses these additional sets of atomic coordinates, but that they are not included in the specification which consequently causes a lack of scope of enablement of the instant invention for one of ordinary skill in the art. M.P.E.P. 2163.04 states "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required."

According to M.P.E.P. §2164.01, "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination as to whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the art to make and use the claimed invention." Applicants

Application No.: 09/815,341  
Art Unit: 1631

-3-

respectfully point out that Claim 21 is a method claim and step (a) is directed to obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein. As argued in the Reply filed July 8, 2004, Applicants have taught how to obtain the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein, how to use said atomic coordinates to define the active subsite of Tie-2, how to solve the crystal structure of a polypeptide comprising the catalytic domain of a Tie-2 protein, how to define the active subsites using various computer programs and methods of identifying a compound which bind to one or more active subsites.

In Example 2, Applicants have exemplified all steps of claim 21 by identifying a compound which is an inhibitor of Tie-2 by obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein, using these atomic coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more active subsites and inhibit the Tie-2 protein.

Claim 21 is directed to a method of identifying compounds which are inhibitors of a Tie-2 protein, the first step of which is obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein. The polypeptide must at a minimum include the catalytic domain of the Tie-2 protein, but may include additional amino acid residues. Applicants have enabled finding atomic coordinates of an unbound Tie-2 polypeptide as well as an entire Tie-2 polypeptide and Inhibitor III complex containing the catalytic domain of a Tie-2 protein.

The Examiner states "[d]ue to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation." Applicants maintain that the Examiner needs to show specific reasons why other embodiments within the full scope of claim 21 would not work, rather than merely alleging the "unpredictability" of crystallizing proteins. "A general allegation of 'unpredictability in the art' is not a sufficient reason to support a rejection for lack of adequate written description." M.P.E.P. 2163.04.

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art: Ansul Co. v. Uniroyal, Inc., 4 F.2d 872 (2d Cir. 1971). "The test is not merely quantitative, since a considerable amount of experimentation is permissible,

Application No.: 09/815,341  
Art Unit: 1631

-4-

if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 52 CCPA 1593, 347 F.2d 574, 146 USPQ 218 (1965); *In re Colonianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

The instant specification teaches crystallization conditions for diphosphorylated Tie-2 802-1124 and Table II on pages 53-56 lists crystallization conditions for Tie-2/inhibitor complexes. The amount of experimentation required to utilize the instant invention is routine in the field of protein crystallography, and, thus, is not undue. One of ordinary skill in the art of protein crystallization knows the steps needed to crystallize a protein. If a crystal does not form, one of ordinary skill in the art would know which parameters to adjust in order to affect the result.

Applicants have enabled claims 21-27, 32 and 33 because not only have Applicants provided crystallization conditions but the knowledge needed regarding how to regulate the crystallization conditions is generally available, as evidenced by the 1991 publication of *Crystallization of Membrane Proteins*, submitted with the Reply filed July 8, 2004. "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94, (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Thus, through examples and teachings throughout the instant specification Applicants have enabled the instant invention. Applicants have taught all of the steps of claim 21 and enabled others to utilize the claimed method to identify compounds which are inhibitors of a Tie-2 protein.

Based upon the foregoing, the rejection of claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, for lack of scope enablement is obviated and should be withdrawn.

Application No.: 09/815,341  
Art Unit: 1631

-5-

The Examiner has rejected Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the invention was filed, had possession of the claimed invention. The Examiner alleges that "due to the open claim language of 'comprises' in claim 21, this claim is directed to encompass amino acid sequences that do not meet the written description provision of 35 U.S.C. §112, first paragraph." Applicants respectfully traverse this rejection. Applicants maintain the arguments presented in the Reply filed December 23, 2003.

The Examiner cites *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 in which the Board held that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Applicants' written description clearly conveys that Applicants had possession of the instant invention at the time of filing. Applicants described the claimed invention with limitations using words and formulas. Applicants provide the atomic coordinates for the crystals, which is the equivalent of drawing a chemical structure.

One of ordinary skill in the art of protein crystallography would understand the written description and claims as filed by Applicants. The application as originally filed provided adequate written description for the claims as originally filed. Applicants have crystallized approximately 95% of the cytoplasmic domain of Tie-2. By crystallizing the catalytic domain Applicants have defined the important part of the Tie-2 protein. Only 30 amino acids, the sequence of which are known, are missing from the N-terminus of Applicants' crystal. Applicants respectfully direct the Examiner's attention to M.P.E.P. §2163, which states:

Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Fauling Inc.*, 230 F.3d 1320, 1323, 57 USPQ2d 1481, 1483 (Fed. Cir. 2000).

Application No.: 09/815,341  
Art Unit: 1631

-6-

Applicants have reduced the instant invention to practice. Specifically, Applicants have shown how to solve the crystal structure of a polypeptide comprising the catalytic domain of a Tie-2 protein, how to define the active subsites using various computer programs and Applicants teach inhibitor docking. In Example 2, Applicants have demonstrated identifying a compound which is an inhibitor of Tie-2 by obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein, using these atomic coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more active subsites and inhibits the Tie-2 protein. Applicants have shown sufficient examples to demonstrate that the instant method works. Applicants' written description, through text, formulas and working examples, convey that Applicants had possession of the full scope of the invention at the time the instant application was filed.

There is no difference between claim 21 and a method claim directed to use of a compound described by a chemical genus, or even a composition of matter claim directed to a chemical genus, in that an Applicant is not required to provide a working example of every possible embodiment covered by the claim. As Applicants stated in the Reply filed December 23, 2003, there is no a requirement as to how many working examples must be provided in a patent application. As stated above, in the instant application Applicants have shown how to solve the crystal structure of a polypeptide comprising the catalytic domain of a Tie-2 protein, how to define the active subsites and taught inhibitor docking, all leading to identifying further inhibitors. Applicants have provided crystallization conditions for Tie-2/inhibitor complexes. Applicants have provided a written description for the instant invention.

The Examiner cites *Fiers v. Revel*, 25 USPQ2d 1601, 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 to support her allegation that "[a]dequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required." Neither of these cases is on point. The claim at issue in *Fiers* was directed to a DNA. Claim 21 in the instant application is directed to a method. Applicants have described the steps of the method and taught how to perform the steps of the method. As discussed above in the response to the Examiner's citation of *Vas-Cath*, Applicants provide the atomic coordinates for the crystals, which is the equivalent of drawing a chemical structure. Thus, Applicants have provided specific written description of the invention.

Application No.: 09/815,341  
Art Unit: 1631

-7-

With respect to *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, the case involved production of EPO and whether the defendant had disclosed the best mode and had enabled the claims. This case also is not on point. There was no question as to whether the defendant had provided adequate written description. The claim at issue in *Amgen* is directed to a DNA sequence. Claim 21 in the instant application is directed to a method of identifying a compound which is an inhibitor of Tie-2.

The Examiner also cites *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 with regard to the lack of written description. In *University of California v. Eli Lilly and Co.* the Board held "[i]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass." The Board further held "[a] description of a genus cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under §112, P1, by showing the enablement of a representative number of species within the genus. See *Angstadt*, 537 F.2d at 502-03, 190 USPQ (BNA) at 218 (decided that applicants 'are not required to disclose every species encompassed by their claims even in an unpredictable art' and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process);...". This case is not on point because it deals with DNA, whereas the instant application is directed to a method of identifying a compound which is an inhibitor of Tie-2.

The Examiner states that because the method contains reference to a polypeptide the same general principals of *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.* and *University of California v. Eli Lilly and Co.* apply. Applicants respectfully point out that in each case the claims in question involved DNA, whereas claim 21 of the instant application is directed to a method. The polypeptide referred to in the claim is not the invention. The invention is the method. Applicants have satisfied the written description requirements for the method of claim 21 by showing possession of the invention, describing the invention in detail and reducing it to practice.

Based upon the foregoing, the rejection of Claims 21-27, 32 and 33 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the

Application No.: 09/815,341  
Art Unit: 1631

-8-

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention, is obviated and should be withdrawn.

The Examiner has rejected claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)). Applicants respectfully traverse this rejection. Applicants maintain the Replies filed December 23, 2003 and July 8, 2004.

The Examiner states that Chen et al. describe a method for identifying an agent that diminishes the activity of a protein (col. 4, lines 56-60). In fact, Chen et al. describes a method for identifying a drug that affects the ability of STAT to *induce expression of a gene* under the control of a promoter containing a binding site for STAT, whereas the instant application is directed to a method of identifying a compound which is an inhibitor of a Tie-2 protein. Chen et al. involves inducing gene expression whereas gene expression is not a part of the instant invention. Chen et al. also do not teach or suggest the step of obtaining the atomic coordinates of a Tie-2 protein.

The Examiner states "[t]he MPEP indicates that descriptive material unable to exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106, section VI)." Applicants respectfully point out that claim 21 is directed to a method, not the atomic coordinates themselves. The Examiner again refers to the atomic coordinates of the Tie-2 protein as nonfunctional descriptive material. Applicants respectfully point out that the atomic coordinates which define the active subsites of Tie-2 to define the structure of the Tie-2 protein. The coordinates are equivalent to a drawn chemical structure. Without the coordinates one cannot envision the structure of the Tie-2 protein or identify compounds which will bind to the specific active subsites. The atomic coordinates are functionally related to both the crystal polypeptide, from which they are obtained, and the compound which is identified based upon the atomic coordinates. Without the atomic coordinates, one would not be able to design a compound made to inhibit the Tie-2 protein. The details of docking results depend intimately from the functional results computed from these coordinates. Using the atomic coordinates in this way is functionally equivalent to ascertaining the structure of an organic compound and using it as a basis for making further analogs. The atomic coordinates are not separable from the method of designing the inhibitor.

Application No.: 09/815,341  
Art Unit: 1631

-9-

Based upon the foregoing, the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) over Chen et al. in view of *In re Gulack* is obviated and should be withdrawn.

The Examiner has rejected claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860). Applicants respectfully traverse this rejection and maintain the arguments presented in the Replies filed December 23, 2003 and July 8, 2004.

As argued above in the rejection of claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), Chen et al. describes a method for identifying a drug that affects the ability of STAT to induce expression of a gene under the control of a promoter containing a binding site for STAT whereas the instant application is directed to a method of identifying a compound which is an inhibitor of a Tie-2 protein. Also as argued above, the atomic coordinates do have a functional relationship to the invention. Without said coordinates, one would be unable to use the instant invention, i.e. identify compounds which act as inhibitors of Tie-2.

With respect to Ziegler (P/N 5,447,860), which the Examiner states "...the sequences of ork (as stated by Ziegler) and Tie-2 (as stated in the instant invention) appear to be the same...", Applicants respectfully point out that the context of Ziegler makes clear that Ziegler refers to the biological ligand of Tie that binds to the extracellular domain, not the small molecule ligands that bind to the catalytic domain of Tie-2. Step (a) of claim 21 is directed to obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of Tie-2. The catalytic domain is inside the cell, as opposed to the extracellular domain, which is outside the cell. Ziegler does not include the catalytic domain of Tie-2. Applicants further note that Ziegler teaches that ork is not Tie. Ziegler provides a novel protein kinase. It teaches and suggests nothing about identifying compounds to inhibit said protein kinase, much less doing it using crystal coordinates.

In the Advisory Action the Examiner states that Applicants' statement that the Ziegler patent refers to the biological ligand of Tie that binds to the extracellular domain, and not the small molecular ligands that bind to the catalytic domain of Tie-2 is unpersuasive. The Examiner further states that "...instant claim 21, do[es] not state that the compound must bind to the



Application No.: 09/815,341  
Art Unit: 1631

-10-

catalytic domain of Tie-2." However, claim 21 is directed to identifying a compound, not a biological ligand. Ziegler does not teach or suggest small molecular ligands.

With respect to *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594), neither Ziegler nor Chen et al., alone or in combination, teach or suggest Applicants' method of identifying inhibitors of Tie-2 proteins. Chen et al. is limited to STAT protein. Neither reference teaches or suggests using atomic coordinates to define the active subsite of Tie-2. One would not be motivated to look to these references to arrive at Applicants' invention.

Based upon the foregoing, the rejection claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen et al (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) and Ziegler (P/N 5,447,860) is obviated and should be withdrawn.

The Examiner has rejected claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (P/N 6,160,092) in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594). Applicants respectfully traverse this rejection. Applicants maintain the Replies filed December 23, 2003 and July 8, 2004.

The Examiner has not established a *prima facie* case of obviousness in any of the foregoing rejections. In order to establish a *prima facie* case of obviousness, first there must be some suggestion or motivation to modify the reference cited by the Examiner. Second, there must be a reasonable expectation of success. One would not look to Vikkula et al., which describes mutations in the kinase domain of Tie-2 that result in increased activity of Tie-2 and that an activating mutation in Tie-2 causes venous malformations, for guidance on a method to identify compounds that inhibit Tie-2 proteins. Further, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Neither Vikkula et al. nor Chen et al. alone or in combination teach or suggest a method of identifying compounds that inhibit a Tie-2 protein using crystal coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more of these active subsites.

To establish a *prima facie* case of obviousness, the invention must be considered as a whole, there must be some suggestion or motivation to modify the reference, the reference must teach or suggest all of the claim limitations and there must be a reasonable chance of success. The Examiner has not provided any motivation to modify Vikkula et al. Further, Vikkula et al. does not teach or suggest all of the limitations of Applicants' claims. As stated in M.P.E.P.

Application No.: 09/815,341  
Art Unit: 1631

-11-

2143.03, "To establish prima facie obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Even if *Vikkula et al.* and *Chen et al.* were combined, they do not teach or suggest a method of identifying compounds that inhibit a Tie-2 protein using crystal coordinates to define the active subsites of Tie-2 and identifying a compound which binds to one or more of these active subsites.

No such motivation or suggestion exists in *Vikkula et al.* When the prior art fails to suggest the claimed invention as a whole, as it does here, any reconstruction of the prior art to obtain that invention necessarily and inevitably requires impermissible hindsight.

The same arguments as made above in response to the rejections of claims 21, 22 and 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over *Chen et al.* (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)) and claims 21-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over *Chen et al.* (P/N 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) apply to this rejection as well.

With respect to *Vikkula et al.*, Applicants respectfully point out that the claims under rejection are directed to a method of identifying a compound which is an inhibitor of a Tie-2 protein. Said method is comprised of specific steps that are listed in claim 21. *Vikkula et al.*, on the other hand, discloses that mutations in the kinase domain of Tie-2 result in increased activity of Tie-2 and that an activating mutation in Tie-2 causes venous malformations. *Vikkula et al.* does not teach or suggest Applicants' method to identify a compound that inhibits Tie-2.

The Examiner states that "*Vikkula et al.* describes a Gen Bank accession number L06139 (see GenBank reference with both nucleic acid and polypeptide translation) which is nucleic acid sequence of human Tie-2 protein (page 1183, col. 2, first paragraph) that is 100% identical to the residues 802-1124 of the sequence in the instant invention." Nonetheless, *Vikkula et al.* alone or in combination with *Chen et al.* (P/N 6,160,092) do not teach or suggest Applicants' method of obtaining atomic coordinates and using said atomic coordinates to obtain a compound that is an inhibitor of a Tie-2 protein.

Based upon the foregoing, Applicants believe the rejection of claims 21-27 under 35 U.S.C. §103(a) as being unpatentable over *Chen et al.* (P/N 6,160,092) in view of *Vikkula et al.* (*Cell*, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) is obviated and should be withdrawn.

Application No.: 09/815,341  
Art Unit: 1631

-12-

Based upon the foregoing, Applicants believe that claims 21-27, 32 and 33 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

Date: September 8, 2004



**Gayle B. O'Brien**  
Agent for Applicants  
Reg. No. 48,812

Abbott Bioresearch Center  
100 Research Drive  
Worcester, MA 01605  
(508) 688-8053